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CORRESPONDENCE

Letters to the Editor

Is Cardiorespiratory Fitness a Unique Cardiovascular Disease Risk Factor?

The paper by Berry et al. (1) provides important data about benefit of fitness measurement. The key question is whether the association of fitness is unique to cardiovascular disease (CVD) or total mortality (2–4). Previous studies from the Cooper Clinic cohort suggest that "fitness" is a measure of total mortality, including reduced cancer mortality (3,4). Second, what is the potential selection bias for participants in the Cooper Clinic evaluation: perceived or known clinical CVD versus exercises? Did any of the questionnaires rate the mean "health status" at baseline? It would have been useful in their paper if the authors had first provided data on the association of non-CVD mortality by fitness and, second, had determined within the CVD group whether there was a relationship of fitness test with ischemic electrocardiographic responses on exercise testing, especially among never cigarette smokers, and subsequent outcomes (2).

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Reply

We appreciate the thoughtful comments from Dr. Kuller on our recent study (1) demonstrating the contribution of measured fitness in midlife to the lifetime risk for cardiovascular disease (CVD) mortality. He raises important questions regarding: 1) the contribution of fitness to both CVD and non-CVD mortality; 2) the generalizability of the findings from the CCLS (Cooper Center Longitudinal Study); and 3) the consistency of the findings across individuals with an abnormal electrocardiography (ECG) response.

First, as Dr. Kuller points out, fitness is associated with both CVD and non-CVD mortality. In the present study, compared with low fitness in mid-life, high fitness was associated with both lower CVD mortality (13.1% vs. 33.1%) and non-CVD mortality (22.3% vs. 34.9%) using the standard Kaplan-Meier cumulative incidence estimate that ignores competing risks. The very purpose of the present study was to determine the association between fitness and CVD mortality after taking into account competing risks from non-CVD mortality. After adjustment for the competing risks in our methods, we see that the association between low fitness and CVD death is attenuated by nearly 20% (adjusted cumulative incidence 27% vs. unadjusted cumulative incidence of 33.1%). Therefore, the adjustment for competing risks from non-CVD death provides a more conservative and more realistic estimate of the association between fitness in mid-life and long-term risk for CVD death.

Second, we believe that the estimates reported in the present study are representative of the general population, particularly for men at ages 55 and 65 years. As we reported in Table 2 in our paper (1), the association between the burden of traditional risk factors and lifetime risk for CVD mortality in the CCLS was strikingly similar to those observed in the Lifetime Risk Pooling Project, a combined analysis from 16 representative cohorts. Thus, although the burden of risk factors is lower in the CCLS, the effect of these risk factors is quite similar to other, more representative cohorts.

Finally, in the present study, we sought to extend our prior lifetime risk work and therefore did not exclude the small number of participants with an abnormal ECG response to exercise (7%). Nevertheless, the contribution of abnormal ECG response to fitness in this dataset is limited. Recently, we reported a systematic analysis of the contribution of fitness to CVD risk prediction (2). In this study, we observed that the incremental contribution of fitness to the net reclassification index was similar across all subgroups, including those with and without an abnormal ECG response.

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Sex-Specific Outcomes for HeartMate II

We read with great interest the recent paper by Starling et al. (1), which provides results on the post-marketing study required by the Food and Drug Administration (FDA) as a condition of approval of the HeartMate II (Thoratec Corporation, Pleasanton, California). However, the value of this report would be strengthened considerably if the authors would provide sex-specific data for the 38 women (22% of the patient population) in the registry.

Although the FDA requires sex-specific data for all high-risk device approvals, a recent analysis found that only 41% of recent cardiovascular device Summaries of Safety and Effectiveness Data reported such data (2). The HeartMate II was approved based on data in just 44 women (3). Furthermore, the FDA's Summary of Safety and Effectiveness Data noted that women had an 18% risk of stroke versus 6% in men and trends toward greater bleeding and infection, although it was not possible to make conclusions on differences in safety between men and women (4). Therefore, the FDA specifically stated that the required post-approval study (INTERMACS [Interagency Registry for Mechanically Assisted Circulatory Support]) would collect data on "gender-specific outcomes." Given that sex-specific outcomes was an FDA condition and that the device has been specifically advertised as being suitable for women (5), we believe the authors should report sex-specific results, which would be particularly helpful for the outcomes in Figures 2 and 3 and adverse events in Table 3. Adequate sex-specific data will help to clarify any differences in outcomes between men and women (6) and enable better care of all patients with advanced heart failure.

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Reply

On behalf of the authors, we thank Drs. Dhruva and Redberg for their letter in reference to our paper (1). We strongly acknowledge the importance that women are well represented in clinical trials and that sex-specific outcomes are reported. Indeed, the newer axial flow pumps have now enabled a wider dissemination of left ventricular assist devices (LVADs), because prior devices were limited to patients with body surface areas >1.5 m^2. We reported a consecutive group of patients implanted with the HeartMate II (HMII) (Thoratec Corporation, Pleasanton, California) device and the previously-approved Federal Drug Administration devices as per a stipulated post-market approval study.

Of the 169 HMII patients, there were 131 men (78%) and 48 women (22%). The percentage of patients who were transplanted, recovered, or received ongoing support at 180 days was 90% for men and 92% for women. A smaller percentage of women (24%) received transplants by 12 months of support compared with men (39%), and a larger percentage were still on LVAD support (63% women vs. 47% males) at 12 months. However, there was no difference in overall survival (log rank $p = 0.4038$), and the 1-year survival estimate for patients remaining on LVAD support was $83.8 \pm 6.7\%$ (women) versus $88.3 \pm 3.0\%$ (men). There were no statistically significant differences in any adverse event between women and men. The control group had a smaller percentage of women (17% vs. 22%), but this was not statistically significant ($p = 0.217$). In comparison with results in the clinical trial for bridge to transplantation for the HeartMate II LVAD in 465 patients as reported by Bogaev et al. (2), the distribution of women (22%) and 361 men (78%) was the same. In addition, similar to the post-approval study, there was a smaller percentage of women receiving heart transplants over the first 18 months of support and a greater percentage with ongoing support compared with men, and also with no difference in overall survival. In contrast to the post-approval study, in the clinical trial, hemorrhagic stroke occurred more frequently in women versus men, and device-related infections occurred less frequently than in men.

Finally, it should be noted that historically, the percentage of women undergoing cardiac transplantation has been significantly lower than men. The latest international heart transplant registry report shows: men, 80.1% from 1992 to 2001 and 77.1% from 2002 to 2006/2009; $p < 0.0001$ (3). We fully agree with Drs. Dhruva and Redberg of the importance to collect and report